Ofev (nintedanib)
Policy Number: C16583-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
6/1/2015	10/09/2019	10/09/2020
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
J8499 (NOC)	RxPA	Q4 2019 20191030C16583-A

PRODUCTS AFFECTED:
Ofev (nintedanib)

DRUG CLASS:
Pulmonary Fibrosis Agents - Kinase Inhibitors

ROUTE OF ADMINISTRATION:
Oral

PLACE OF SERVICE:
Specialty Pharmacy
The recommendation is that medications in this policy will be for pharmacy benefit coverage and patient self-administered

AVAILABLE DOSAGE FORMS:
Ofev CAPS 100MG Ofev CAPS 150MG

FDA-APPROVED USES:
Treatment of idiopathic pulmonary fibrosis, Systemic sclerosis-associated interstitial lung disease

COMPENDIAL APPROVED OFF-LABELED USES:

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS:
Definitive idiopathic pulmonary fibrosis (IPF) confirmed by a pulmonologist, radiologist, and/or pathologists experienced in the diagnosis of interstitial lung disease

REQUIRED MEDICAL INFORMATION:
A. IDIOPATHIC PULMONARY FIBROSIS

1. Documented diagnosis of IPF confirmed by the presence of usual interstitial pneumonia (UIP) via high-resolution computed tomography (HRCT) AND/OR Surgical lung biopsy. Submit chest HRCT study OR pathology report if a surgical lung biopsy was performed AND
2. Member does not have other known causes of interstitial lung disease. Documentation of workup required:
    1) No significant environmental exposure known to cause pulmonary fibrosis (e.g. drugs, asbestos, beryllium, radiation, raising birds/livestock, and metal), OR

2) No known explanation for interstitial lung disease (e.g. radiation, sarcoidosis,
hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia, human immunodeficiency virus (HIV), viral hepatitis, and cancer), OR
3) No diagnosis of any connective tissue disease known to cause interstitial lung disease (e.g. scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis)
AND

3. Documented baseline of both of the following (dated within the prior 30 days):
   1) Forced Vital Capacity (%FVC) is 50 to 90% [≥ 50% and ≤ 90%] of predicted
   AND
   2) Carbon monoxide diffusion capacity of the lung (DLCO) of 30-90% of predicted [≥ 30% and ≤ 90%]
   AND
4. Documentation of a liver function test within the past 30 days confirming that member does NOT have ANY of the following (including ALT, AST, and bilirubin): Significant impaired liver function [ALT/AST more than 3 times the upper limit of normal (ULN); total bilirubin greater than the ULN; alkaline phosphatase greater than 3 times the ULN]; moderate/severe hepatic impairment (Child- Pugh class B or C); or end-stage liver disease
   AND
5. Prescriber attests that patient is a Non-smoker, or has been abstinent from smoking for at least six weeks
   AND
6. Female and of child-bearing age: Documentation of a negative pregnancy test prior to initiation of treatment AND counseling regarding adequate contraception to prevent pregnancy during treatment and for at least 3 months after taking their last dose of nintedanib
   AND
7. Prescriber attests that Esbriet (pirfenidone) will not be used concurrently with Ofev (nintedanib)

B. SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE:

1. Documented diagnosis of systemic-sclerosis- associated interstitial lung disease based upon the 2013 American College of Rheumatology / European League Against Rheumatism classification criteria- see appendix [DOCUMENTATION REQUIRED]
   AND
2. Documentation that onset of disease is less than 7 years from request OR 10% fibrosis on a chest high resolution computed tomography (HRCT) scan conducted within the previous 12 months. [DOCUMENTATION REQUIRED]
   AND
3. Documentation of FVC greater than or equal to 40% of predicted AND a DLCO 30-89% of predicted. [DOCUMENTATION REQUIRED]
   AND
4. Prescriber attests that patient has tried and failed, has a labeled contraindication or will be concurrently taking mycophenolate mofetil
   AND
5. Prescriber attests that patient is a Non-smoker, or has been abstinent from smoking for at least six weeks

DURATION OF APPROVAL:
Initial authorization: 3 months

Continuation of therapy authorization: 6 months

QUANTITY:
60 capsules per 30 days (300 mg/day)

PRESCRIBER REQUIREMENTS:
Prescribed by, or in consultation with, a board-certified pulmonologist. Submit consultation notes if applicable. If Prescriber is not a pulmonologist, pulmonary specialty follow-up should occur at least biannually for assessment of drug response.

AGE RESTRICTIONS:
IDIOPATHIC PULMONARY FIBROSIS: ≥ 40 years of age
SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE: 18 years of age or older

GENDER:
Male and female

CONTINUATION OF THERAPY:
A. IDIOPATHIC PULMONARY FIBROSIS

1. Documentation that member currently meets ALL initial coverage criteria and remains a candidate for treatment based upon the Prescriber's assessment while on therapy
   AND
2. If Prescriber is not a pulmonologist, pulmonary specialty follow-up should occur at least biannually for assessment of drug response. Consultation notes (if applicable) must be submitted for each continuation of treatment request.
   AND
3. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance)
   AND
4. Member continues to receive monitoring of liver function as recommended within the labeling* NOTE: *Monthly for first 6 months, and every 3 months thereafter, or as clinically required
   AND
5. Documentation of stabilized or improved condition as indicated by 1 of the following:
   1) < 10% decline in percent predicted FVC [NOTE: A >10% decline in FVC over a 12 month period indicates disease progression and continuation of treatment will not be authorized], OR
   2) < 15% decline in predicted DLCO during a 6-month period
   AND
6. Documentation that member has remained tobacco-free
   AND
7. Member continues to NOT have contraindications to Ofev (nintedanib) therapy [including: significant hepatic impairment (Child-Pugh C), significantly impaired kidney function (GFR or CrCl less than 30 mL/min) or end-stage renal disease requiring dialysis]

B. SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE:

1. If Prescriber is not a pulmonologist, pulmonary specialty follow-up should occur at least biannually for assessment of drug response. Consultation notes (if applicable) must be submitted for each continuation of treatment request.
   AND
2. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance)

AND
3. Member continues to receive monitoring of liver function as recommended within the labeling* NOTE: *Monthly for first 6 months, and every 3 months thereafter, or as clinically required
AND
4. Documentation of stabilized or improved condition as indicated by 1 of the following:
(a) < 10% decline in percent predicted FVC [NOTE: A >10% decline in FVC over a 12 month period indicates disease progression and continuation of treatment will not be authorized],
OR
(b) < 15% decline in predicted DLCO during a 6-month period

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Ofev (nintedanib) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy

Contraindications include: Hypersensitivity to pirfenidone or any of the active ingredients (e.g., gelatin, microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate, shellac, iron oxide black, iron oxide red, iron oxide yellow, titanium dioxide, propylene glycol, ammonium hydroxide)

Exclusions for coverage include, but are not limited to:
1. Concurrent use of with Esbriet (pirfenidone) NOTE: Ofev (nintedanib) has not been studied in combination with nintedanib (Ofev); therefore, concomitant therapy will not be authorized
2. Moderate/severe hepatic impairment (Child-Pugh C), end-stage liver disease, or a history of end-
stage renal disease requiring dialysis
3. Active infection (e.g. bronchitis/bronchiolitis, pneumonia, and sinusitis)

OTHER SPECIAL CONSIDERATIONS:
The two Phase III (INPULSIS-1 and INPULSIS-2) trials which the FDA approval of nintedanib was based upon included only patients 40 years of age or older.

Forced vital capacity (FVC): Nintedanib has only been studied in subjects with mild-to-moderate IPF (percent predicted FVC greater than 50% and a percent predicted DLCO between 30-79%). The safety and efficacy in patients with more severe IPF disease is unknown. There is little data to indicate to what extent nintedanib is effective in patients with severe IPF (FVC < 50%).

Carbon monoxide diffusing capacity (DLCO): All patients included in the studies had a clinically and radiologically confirmed diagnosis of IPF and mild-to-moderate disease, with a baseline percent predicted FVC ≥ 50% and percent predicted DLCO 30% to 79%. The safety and efficacy in patients with more severe disease is unknown.

Liver function tests (ALT, AST, and bilirubin) should be conducted prior to initiation of treatment and monthly for 3 months, and every 3 months thereafter and as clinically indicated. In clinical trials, Ofev was associated with elevations of liver enzymes that were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. Ofev also associated with increases in bilirubin. The safety and efficacy of Ofev in patients with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment have not been

studied and is therefore not recommended for these patients

Cigarette smokers: Smoking may decrease exposure to nintedanib; members should stop smoking prior to treatment and avoid smoking during therapy.

Pregnancy & Lactation: Based on the mechanism of action and adverse events observed in animal reproduction studies, nintedanib may be expected to cause fetal harm if used during pregnancy. Women of reproductive potential should use adequate contraception during therapy; pregnancy status should be obtained before treatment and pregnancy should be avoided; effective contraception should be used during therapy and for at least 3 months after the last dose. Based on animal studies, nintedanib may reduce female fertility.

Clinical Practice Guidelines

The American Thoracic Society (ATS), through a cooperative assessment with several other international organizations, provides guidance on the diagnosis and treatment of IPF. The official clinical practice guideline of the ATS was approved by the ATS, May 2015, The European Respiratory Society (ERS), April 2015, The Japanese Respiratory Society (JRS), April 2015, AND The Latin American Thoracic Association (ALAT), April 2015

A multidisciplinary, dynamic approach, with the input of clinicians, radiologists, and pathologists has been shown to improve diagnostic accuracy and is strongly recommended. (ATS 2015/ERS/JRS/ALAT)

Requirements for diagnosis of IPF include exclusion of other known causes of interstitial lung disease, presence of a pattern of usual interstitial pneumonia on high resolution CT (HRCT), and/or a specific combination of HRCT findings and lung biopsy findings.

Endpoints for assessing the disease and highlights vital capacity (VC) are one of the factors that can be used to assess response to therapy. A favorable response can be defined as a >10% increase in VC over 3-6 months. A stable response is within a 10% change, positively or negatively from baseline, in VC over 3-6 months. A >10% decrease in VC over that same time period is identified as a failure to respond. (ATS)

Many trials will assess change in forced vital capacity (FVC), usually centering around 10%, and change in carbon monoxide diffusing capacity (DLCO). Clinical practice will similarly monitor these two parameters over time to determine progression of the disease.

The ATS statement does not specifically recommend any one treatment as superior. While there is no guidance on sequential therapies, both nintedanib and pirfenidone are conditionally recommended. The ATS statement identifies conditional recommendations as recognizing that different choices will be appropriate for individual patients and providers should help each patient arrive at a management decision consistent with his or her values and preferences. Providers should explicitly interpret that although drug therapy may slow rate of loss of lung function, this may also not necessarily make an individual patient feel better. (ATS 2015)

BACKGROUND:

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressively fibrosing Idiopathic Interstitial Pneumonias, occurring primarily in older adults, limited to the lungs, and associated with the histopathological and/or radiologic pattern of unspecified interstitial pneumonia (UIP). IPF is a form of chronic interstitial fibrosis that is limited to the lung and is the most common idiopathic interstitial pneumonia, one type of interstitial lung disease, and is characterized

histopathologically by usual interstitial pneumonia. IPF is characterized by the loss of alveolar structure through apoptosis of epithelial and endothelial cells, infiltration of inflammatory cells into interstitial and alveolar spaces, proliferation of fibroblasts, and excessive deposition of interstitial collagens. The cause is unknown; however, fibrosis appears to be preceded and provoked by a chronic inflammatory process. Demographically, males predominate and diagnosis occurs between the fifth and seventh decade of life. Progression of the disease is variable among individuals, ranging from a rapid decline to a steady decrement in lung function that can last several years. Progressive fibrosis ultimately leads to death with a median survival of 3 to 5 years after diagnosis. Clinical manifestations include dyspnea, reduced lung volume, and impaired gas exchange. It is progressive and irreversible, with a mean survival of approximately 2 to 4 years and patients with acute exacerbations have ≥ 60% in-hospital mortality. Complications of IPF include heart failure, pulmonary embolism, pulmonary arterial
hypertension, and lung cancer. Risk factors for IPF include cigarette smoking, genetic variants of a number of genes, exposure to metal and wood dust, and possibly gastroesophageal reflux and exposure to certain viruses.
Pharmacologic treatments have been limited and traditional approaches have included various anti-inflammatory and immunosuppressive agents; however, these approaches do not seem to be effective and are no longer considered part of routine maintenance care. Treatment has predominantly been limited to supportive care, including oxygen therapy and pulmonary rehabilitation. Lung transplantation is also an option for selected patients. Five year survival is approximately 20-30%. Prior to the FDA approval of pirfenidone (Esbriet) and nintedanib (Ofev) in October 2014, no medications were approved for the treatment of IPF. These two agents work by different mechanisms of action, and neither agent is curative, their simultaneous FDA approval in 2014 was based on the potential for nintedanib and pirfenidone to reduce the rate of the inexorable decline in lung function in IPF.

Nintedanib is a kinase inhibitor shown to inhibit the vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, and VEGFR-3), fibroblast growth factor receptor (FGFR1, FGFR2, and FGFR3), and platelet-derived growth factor receptor (PDGFR) alpha and beta. Nintedanib blocked intracellular signaling and prevented proliferation, migration, and transformation of fibroblasts implicated in idiopathic pulmonary fibrosis pathogenesis.

The efficacy and safety of nintedanib was evaluated in two replicate phase 3 trials: INPULSIS-1 and - INPULSIS2. INPULSIS-1 and INPULSIS-2 were identical in design. Both trials were randomized, double-blind, placebo-controlled studies comparing treatment with nintedanib 150 mg twice daily to placebo for 52 weeks in patients with IPF. Patients were randomized in a 3:2 ratio to either nintedanib 150 mg or placebo twice daily for 52 weeks. The primary endpoint was the annual rate of decline in
Forced Vital Capacity (FVC). Nintedanib was found to significantly reduce absolute FVC decline in both trials, however, a <10% decline, which is thought to be evidence of reducing clinical disease progression was significant in only INPULSIS-1 and not in INPULSIS-2. Nintedanib was frequently associated with diarrhea, with a rate of 61.5% treatment group vs 18.6% placebo group in INPULSIS-1, and 63.2% treatment group vs 18.3% placebo group in INPULSIS-2.

Effectiveness is defined as improvement or maintenance (<10% decline in percent predicted FVC or

< 200 ml decrease in FVC) of disease. The primary outcome evaluated was the annual rate of decline in FVC in milliliters (mL). Nintedanib significantly reduced the annual rate of FVC decline compared
with placebo in the INPULSIS-1 (-114.7 vs -239.9 mL) and the INPULSIS-2 (-113.6 vs -207.3 mL) randomized trials (N=1066) of patients 40 years or older diagnosed with idiopathic pulmonary fibrosis within the previous 5 years.

FVC is considered reliable, valid, and responsive measures of disease status as well as independent predictors of survival in patients with IPF. A decline in FVC is consistent with disease progression and is predictive of reduced survival time.

FVC can be used as an objective measure of IPF disease progression, and a ≥10% FVC decline over 12 months has traditionally been used as a predictor of mortality risk. One study showed that a ≥10% FVC decline at 12 months was linked to a ≥2.4x greater risk of mortality.

ATS/ERS/JRS/ALAT Consensus Guidelines (2011) indicate that a change in absolute forced vital capacity (FVC) of 10% [with or without a concomitant change in carbon monoxide diffusing capacity(DLCO)] or a change in absolute DLCO of 15% (with or without a concomitant change in FVC) is a surrogate marker of mortality and is evidence of disease progression

APPENDIX:

Diffusing Capacity for Carbon Monoxide (DLCO)

Carbon monoxide diffusing capacity (DLCO); DLCO measures the ability of the lungs to transfer gas from inhaled air to the red blood cells in pulmonary capillaries

The normal values for CO diffusing capacity vary widely between laboratories, and both absolute values and their reproducibility are largely influenced by the measurement technique.

Therefore, this measurement is most useful if the patient's lung function changes are followed consistently by the same laboratory.

Forced vital capacity (FVC) is a widely used measure of disease status and a common endpoint in clinical trials in patients with idiopathic pulmonary fibrosis. FVC is measured via spiromety.

High-resolution computed tomography (HRCT; also called thin-section CT scanning) provides more detail than either chest radiography or conventional CT scanning, with an overall sensitivity of 95 percent and a specificity approaching 100 percent. Compared to chest radiography, HRCT can more accurately assess the pattern and distribution of diffuse lung disease, which may be beneficial when trying to narrow the differential diagnosis or define a target for lung biopsy.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

REFERENCES:

1. Ofev (nintedanib) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; September 2019
2. American Hospital Formulary Service (AHFS). Drug Information 2019. [STAT!Ref Web site]. Available at: http://online.statref.com. [via subscription only]
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at: http://www.clinicalpharmacology.com. [via subscription only]
4. DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T114208, Idiopathic pulmonary fibrosis; [updated 2018 Dec 05, cited March 2019]. Available from https://www.dynamed.com/topics/dmp~AN~T114208. Registration and login required.
5. Bradley B, Branley HM, Egan JJ, et al. Interstitial lung disease guideline: the British Thoracic

Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax. 2008 Sep;63 Suppl 5:v1-58, correction can be found in Thorax 2008 Nov;63(11):1029, commentary can be found in Thorax 2009 Jun;64(6):548
6. Richeldi, L, du Bois, RM, Raghu, G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. The New England journal of medicine. 2014 May 29;370(22):2071-82. PMID: 24836310
7. Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med. 2011;365(12):1079-1087. PMID: 21992121
8. Richeldi L, Cottin V, Flaherty KR, et al. Design of the INPULSIS trials: two phase 3 trials of nintedanib in patients with idiopathic pulmonary fibrosis. Respir Med. 2014;108(7):1023-1030. Available at: https://clinicaltrials.gov/show/NCT01335464 and http://clinicaltrials.gov/show/NCT01335477
9. Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. Lancet. 2017 May 13;389(10082):1941-52
10. Ofev (nintedanib) formulary submission dossier. Boehringer Ingelheim Pharmaceuticals, Inc. 30 October 2014.
11. Ley B, Collard HR and King TE. Clinical Course and Prediction of Survival in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2011; 183: 431-40
12. Schmidt SL, et al. Predicting pulmonary fibrosis disease course from past trends in pulmonary function. Chest 2014;145:579–585.
13. Wells AU and Ward S (2014) Pulmonary Function Tests in Idiopathic Pulmonary Fibrosis in Meyer KC and Nathan SD (Eds) Idiopathic Pulmonary Fibrosis: A Comprehensive Clinical Guide, pp 103-21 (New York), Humana Press
14. American Thoracic Society Documents: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis- An Update of the 2011 Clinical Practice Guideline. Am J Resp Crit Care 2015; 192(2): e3-e19. Available at: http://www.thoracic.org/statements/resources/interstitial-lung-disease/IPF-Full-length.pdf. Accessed March 2019
15. The revised ATS/ERS/JRS/ALAT diagnostic criteria for idiopathic pulmonary fibrosis (IPF) practical implications. Wells Respiratory Research 2013, 14(Suppl 1):S2 Available at: http://respiratory-research.com/content/14/S1/S2 Accessed March 2019
16. An Official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med Vol 188, Iss. 6, pp 733–748, Sep 15, 2013. Available at: http://www.thoracic.org/statements/resources/interstitial-lung-disease/classification-of-IIPs.pdf Accessed March 2019
17. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. Am J Respir Crit Care Med. 2011 Mar 15;183(6):788-824. DOI:10.1164/rccm.2009-040GL. Available at: https://www.ers- education.org/lrmedia/2011/pdf/193989.pdf Accessed March 2019
18. Raghu, G., Remy-Jardin, M., Myers, J., Richeldi, L., et al. (2018). Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. American Journal of Respiratory and Critical Care Medicine, 198(5), e44-e68. https://doi.org/10.1164/rccm.201807-1255ST Available at: https://www.atsjournals.org/doi/full/10.1164/rccm.201807-1255ST?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&%20-%20readcube-epdf Accessed March 2019